European Journal of Pharmaceutics and Biopharmaceutics 81 (2012) 674–682

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Upscaling of the hot-melt extrusion process: Comparison between laboratory scale and pilot scale production of solid dispersions with miconazole and Kollicoat® IR

Sandra Guns [a], Vincent Mathot [b,c], Johan A. Martens [d], Guy Van den Mooter [a,*]

[a] Laboratory of Pharmacotechnology and Biopharmacy, KU Leuven, Leuven, Belgium
[b] SciTe B.V., Geleen, The Netherlands
[c] Department of Chemistry, KU Leuven, Heverlee, Belgium
[d] Centre for Surface Chemistry and Catalysis, KU Leuven, Heverlee, Belgium

ARTICLE INFO

Article history:
Received 10 February 2012
Accepted in revised form 29 March 2012
Available online 11 April 2012

Keywords:
Hot-melt extrusion
Kollicoat IR
Solid dispersions
Upscaling
Miconazole
Modulated differential scanning calorimetry

ABSTRACT

Since only limited amount of drug is available in early development stages, the extruder design has evolved towards smaller batch sizes, with a more simple design. An in dept study about the consequences of the differences in design is mandatory and little can be found in literature. Miconazole and Kollicoat® IR were used as model drug and carrier for this study. Two series of solid dispersions were made with a laboratory scale (internal circulation-simple screw design) and a pilot scale extruder (continuous throughput-modular screw design). Efforts were made to match the operating parameters as close as possible (residence time, extrusion temperature and screw speed). The samples were analyzed with modulated DSC straight after production and after exact 24 h and 15 days storage at −26 °C. The kinetic miscibility of the samples prepared with the laboratory scale extruder was slightly higher than the samples prepared with the pilot scale extruder. As the solid dispersions with high drug load were unstable over time, demixing occurred, slightly faster for the samples prepared with the laboratory scale extruder. After 15 days, the levels of molecular mixing were comparable, pointing to the predictive value of samples prepared on laboratory scale.

1. Introduction

Hot-melt extrusion is a well-investigated manufacturing technology in plastics industry since the beginning of the 20th century [1]. Although pharmaceutical-class extruders are virtually identical to plastics extruders, some adaptations were made to meet the regulatory requirements in the pharmaceutical industry. In pharmaceutical research, hot-melt extrusion is a technology platform that provides the opportunity to intensively mix a drug with a carrier at elevated temperatures in a continuous mode, without the need of a solvent, and thereby creating a solid dispersion which is able to tune the bioavailability of the incorporated drug. Numerous examples of immediate- and sustained-release formulations prepared by hot-melt extrusion can be found in literature [2,3]. Some of these studies are performed with a single screw extruders [4,5], mainly because of their more simple design and more reasonable cost [2,6]. Nevertheless most studies use a co-rotating twin-screw extruder [7–10]. Twin-screw extruders have several advantages over single screw extruders, such as easier material feeding, high kneading and dispersing capacities, less tendency to over-heat and shorter transit time. The benefit of a co-rotating system is that they are self-wiping as they are generally of the intermeshing design. They can be operated at high screw speeds and achieve high outputs, while maintaining good mixing and conveying characteristics. Unlike counter-rotating extruders, they generally experience lower screw and barrel wear as they do not experience the outward "pushing" effect due to screw rotation [11].

The opportunity to control the shape of the end product has made that hot-melt extrusion can be used both for oral applications [5,7–10,12,13] as well as for implants [14] and patches [4,15], depending on the downstream processing. Although hot-melt extrusion is a promising technique for various applications, the major disadvantage of the hot-melt extrusion techniques is the use of heat and the application of shear forces on the active pharmaceutical ingredient (API), which limits its use to heat stable compounds only. One must remark that this drawback must be toned down because of the limited residence time of the material inside the extruder.

* Corresponding author. Laboratory of Pharmacotechnology and Biopharmacy, KU Leuven, Gasthuisberg O&N2, Herestraat 49, Box 921, 3000 Leuven, Belgium. Tel.: +32 16 330 304; fax: +32 16 330 305.
E-mail address: Guy.VandenMooter@pharm.kuleuven.be (G. Van den Mooter).

0939-6411/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejpb.2012.03.020

In general, an extruder exists of three stages that can further be extended with downstream processing equipment for cooling, cutting and/or collecting the finished product. The first is a feeding stage. A hopper either feeds the material in the extruder by starve feeding (by means of gravity) or by flood feeding (preset mass flow rate). Hereby the material enters the second stage that consists of a heated barrel wherein the screws rotate. This zone is responsible for the conveying, melting and mixing of the material. After this stage, the material passes through a die, which allows shape formation [11].

A major obstacle in drug development today is the low aqueous solubility of new API's related to complex molecular structures [16]. Various techniques have been described to improve the solubility and bioavailability of API, including solid dispersions prepared via hot-melt extrusion. Subsequently it is important to assess the appropriateness of hot-melt extrusion as processing method for a new drug candidate as soon as possible. As only limited amounts of API are available in the early development stages, the extruder design has evolved towards smaller batch sizes (5–20 g or even lower). These small-batch extruders often posses a more simple design with respect to screw configuration and in most cases have an internal circulation channel. This makes upscaling to production size extruders working in continuous mode extremely challenging [17]. In literature, different terms are used to describe the extruder type. The laboratory scale extruder described in this paper is a mini-extruder with simple screw design, an internal circulation channel and a production batch size of 5cc. The pilot scale extruder is an extruder with modular screw design, a continuous throughput and can produce up to 8 kg/h (depending on operating parameters and material that is processed). Although this last type is often referred to in literature as a laboratory scale extruder, we believe it is more convenient to address it as a pilot scale extruder considering the similarity with the production scale extruders used in industry today and the relative high throughput.

Despite the discrepancy in design between laboratory scale extruders and pilot or production scale extruders, laboratory scale extruders are popular in early development and in research [7,12,13,17–19]. An in dept study about the consequences of the difference in design is mandatory and little can be found in literature. Therefore, we performed a study were we made a series of solid dispersions with poly(ethyleneglycol-g-vinylalcohol) (EG/VA) as a carrier and miconazole as model drug with both extruder types. Efforts were made to match the operating parameters as close as possible (like residence time, extrusion temperature and screw speed) to see the true impact of the extruder design on the mixing behavior of the two types of extruders. The goal was to evaluate the predictive value of these small batch size laboratory scale extruders for the manufacturing of solid dispersions. Samples were evaluated with modulated differential scanning calorimetry (MDSC) straight after production, but also after 24 h and 15 days, to study the possible demixing of unstable solid dispersions.

The carrier EG/VA selected for this study has been thoroughly characterized and has shown before to be a potential carrier for the formulation of solid dispersions [20–22]. It consists of two semi-crystalline fractions: a polyethylene glycol (PEG) fraction and a polyvinylalcohol (PVA) fraction. The PEG fraction shows a glass transition temperature at −57 °C and a melting transition at 15 °C, the PVA fraction shows a glass transition temperature around 45 °C and a melting transition at 212 °C. Hot-melt extrusion increases the crystallinity of the PVA fraction [23].

Miconazole was used as a model drug. It has a T_g in between that of the amorphous PEG fraction and the amorphous PVA fraction (T_g(miconazole) = 1.65 °C) [24]. It has been proven before that miconazole and EG/VA can be processed by hot-melt extrusion to make amorphous solid dispersions [22], making this system a suitable model system to study the effect of different scale and types of extruders on the mixing behavior of drugs and polymers.

2. Material and methods

2.1. Material

The graft copolymer of ethylene glycol and vinyl alcohol (Mw = ca. 45,000 Da) was obtained from BASF (Ludwigshafen, Germany). Miconazole was kindly donated by Janssen Pharmaceutica (Beerse, Belgium).

2.2. Methods

2.2.1. Preparation of solid dispersions with a laboratory scale extruder

Solid dispersions were prepared with a 5cc mini compounder (Xplore DSM, Geleen, the Netherlands) with a co-rotating gearbox with respectively 9%, 15%, 20%, 25%, 31%, 35%, 41%, 47% and 50% w/w of miconazole. These samples are referred to as sample L9, L15, L20, L25, L31, L35, L41, L47 and L50 respectively. The core of this extruder is formed by a mixing compartment consisting of two separable halves and double, conical mixing screws. The two metal halves each consist of three controlled heating zones, which were always kept at the same temperature (170 °C). Seven thermocouples are available for temperature monitoring, including one in the melt. The screw speed was set at 200 rpm. Per run, a load of 4.5 g physical mixture was fed manually into the hopper while keeping the screw speed at 50 rpm, and after feeding, the internal circulation time was 1 min at elevated screw speed. The core of the extruder was purged with nitrogen during extrusion. During extrusion, a log was made of the force needed by the extruder to rotate the screws. This is proportional to the torque experienced by the extruder according to the following equation:

$$\boldsymbol{\tau} = \boldsymbol{r} \times \mathbf{F} \tag{1}$$

$\boldsymbol{\tau}$ is torque, $\boldsymbol{r}$ is the displacement vector (a vector from the point from which torque is measured to the point where force is applied), and $\boldsymbol{F}$ is the force vector.

The extrudates were collected without any cooling accessories and analyzed with MDSC within 15 min after production. All samples were stored in a freezer (−26 °C) protected from humidity, and subsequent analyses were carried out at different time points.

To study the effect of shear and operating temperature, two additional samples with 40% w/w miconazole were prepared using the same extruder. The residence time was again one minute, but for the first sample a temperature of 130 °C was used and a screw speed of 200 rpm, while for the second sample, a temperature of 170 °C was used and a screw speed of 400 rpm. The samples were analyzed with MDSC within 15 min after production.

2.2.2. Preparation of solid dispersions with a pilot scale extruder

Solid dispersions were prepared with a twin-screw extruder type MP19PC (APV Baker Limited, Newcastel-U-Lyme, England) with respectively 9%, 18%, 29%, 34%, 39%, 45%, 49%, 56% and 60% w/w of miconazole. These samples are referred to as sample P9, P18, P29, P34, P39, P45, P49, P56 and P60 respectively. A schematic picture of the pilot scale extruder is given in Fig. 1.

Physical mixtures are fed through the feeding system by a rotating screw of which the speed can be controlled (starve feeding). To avoid arching in the feeder hopper, the material was constantly stirred manually. The first zone of the extruder was water cooled. Subsequently, the material passes through two heated zones. In these experiments, the zones two and three were kept at equal temperature (160 °C). When the material has passed the screws, it will leave the extruder through a die which was not particularly